ORIGINAL ARTICLE

Formulation, Development, and Evaluation of Sustained Release Tablet of Ambroxol Hydrochloride

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Abstract

Introduction: Ambroxol hydrochloride tablet was formulated as sustained release tablets employing rice bran wax polymer and the sustained release behavior of the fabricated tablets were investigated. **Materials and Methods:** The objectives of study are Sustained release matrix tablets containing 75 mg ambroxol hydrochloride were developed using different drug polymer ratios of MCC, RBW and DCP. Tablets were prepared by direct compression. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release and by using 23 factorial designs. **Result and Discussion:** The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-completion sustained release for ambroxol hydrochloride, and 98-103% released at the end of 8 h. **Conclusion:** The results of dissolution studies indicated that formulation F7, the most successful of the study, exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets (except F7) showed diffusion-dominated drug release. The mechanism of drug release from F7 was diffusion with erosion.

Key words: Rice bran wax, Ambroxol hydrochloride, sustained release tablet, 2^3 factorial design, and pharmacokinetics

INTRODUCTION

Chronic bronchopulmonary diseases are common health problems that are characterized by abnormal mucus secretion and impaired mucus transport. They are often associated with infectious microorganisms and, thus, treated with potent antibiotics, anti-tuberculosis drugs, and antifungal agents. Mucolytic agents are useful in adjunctive therapy of respiratory tract disorders producing a modest improvement in symptom control and lung function.[1,2]

It has been demonstrated that there is a synergism between mucolytics and antibiotics in the treatment of exacerbation of chronic bronchitis. Moreover, mucolytics act as scavengers of reactive oxygen species over expressed by the body especially during periods of oxidative stress when they can significantly damage cell structures.[3] Ambroxol (trans-4-(2-amino-3,5-dibromobenzyl)-aminocyclohexanol) is an active metabolite of bromhexine that has been used to increase surfactant secretion in the lungs and as mucolytic to breakdown acid mucopolysaccharide fibers making the sputum thinner and less viscous, thus more easily removed by coughing.[4]

Ambroxol has also been reported to have a cough-suppressing effect and anti-inflammatory action through inhibition of mediator release involved in the pathogenesis of allergic inflammation. Therefore, it is frequently used in the treatment

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Received: 27-09-2022
Revised: 16-11-2022
Accepted: 26-11-2022

of bronchial asthma and chronic bronchitis and also used in pulmonary alveolar proteinosis and infant respiratory distress syndrome. It is rapidly absorbed after oral administration with an onset of action that occurs after about 30 min followed by fast elimination with a half-life of 3–4 h only thus requiring three dosing per day for optimum therapeutic efficacy.[5]

This high dosing frequency may increase the risk of exacerbation of gastrointestinal side effects such as diarrhea, heartburn, indigestion as well as intense headaches, shortness of breath and weakness, and possible allergic reactions to the skin. Therefore, several sustained release formulations of Ambroxol have been developed that are based on pellet, tablet dosage forms.[6] Drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Basic goal of the therapy to achieve steady states blood level that is therapeutically effective and nontoxic for an extended period of time.[7,8]

Sustained release systems consist of any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.[9,10] A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations as shown in Figure 1.

MATERIALS AND METHODS

Material

Ambroxol hydrochloride was gifted by the Medley Pharmaceuticals Andheri, Mumbai and rice bran wax was purchased from Balaji Mill Mumbai. Other chemicals such as Di Calcium Phosphate, Magnesium Stearate, and Talc, all the excipients used were of analytical grade, were purchased from Vishal Chemical Mumbai.

Method

Direct compression

Direct compression was followed to manufacture the ambroxol hydrochloride tablets. All the polymers selected, drug and excipients were passed through sieve no. 40 and lubricant was passed through sieve no #60 before using into formulation.[4,11]

Preformulation studies are the first step in the rational development of dosage form of a drug substance.[12] The objective of preformulation studies is to develop a portfolio of information about the drug substance so that this information is useful to develop formulation [Table 1]. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.[13] Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.[14] The color, odor, taste, and appearance of the Drug A were characterized and recorded [Table 2].[15]

The melting point was determined by the capillary method using digital melting point apparatus. The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions.[16]

Assay

5 g of Drug "A" was transferred to a 50 mL volumetric flask; 5 mL of chloroform was added and volume was adjusted with methanol. 0.3 mL of this solution was pipetted out in 100 mL of volumetric flask and adjusted with methanol. The absorbance of this solution was measured and compared with known concentration of Drug "A" of similar dilution at λ max 235 nm in Jasco double-beam spectrometer. Quantity of Drug "A" was calculated using formula 1.00 × C (At/As), in which C is the concentration in mg/ml of Drug "A" in standard solution, At and As are the absorbance's of test and standard solutions, respectively.[17,18]

Stability studies

The purpose of the stability testing is to obtain information

Table 1: Formulation ingredients table

Ingredients	Quantity
Ambroxol hydrochloride	75 mg
Rice bran wax	37.5
MCC	2 mg
DCP	132 mg
Magnesium stearate	1.5 mg
Talc	1.5 mg
Tablet weight	250 mg

Table 2: Organoleptic characteristics of drug "Ambroxol HCL"

S. No.	Parameter	Observation
1	Color	Whitish powder
2	Odor	Odorless
3	Appearance	Crystalline powder
4	Melting point	147–149°C
5	Loss on drying	<0.23% W/W
6	Assay	100.72%

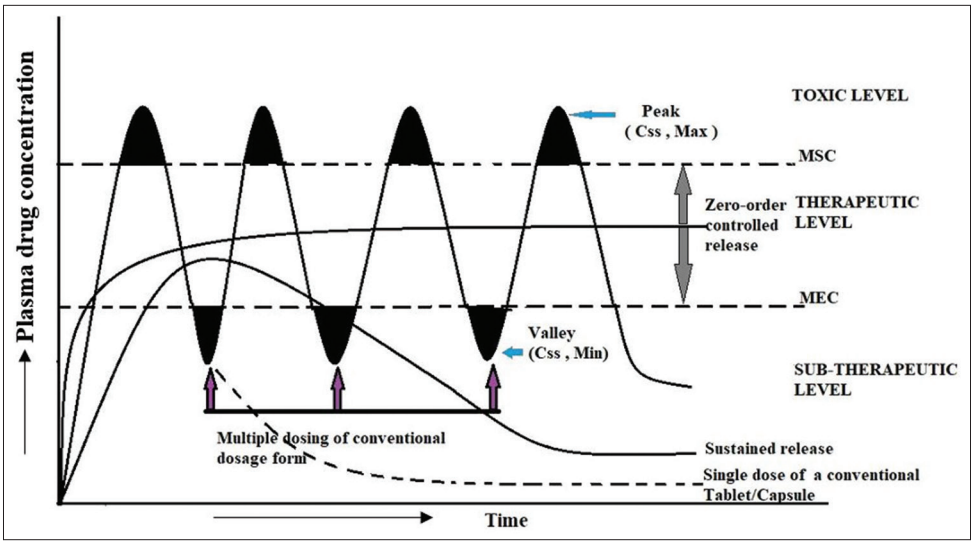

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

Table 3: Preformulation data

Trial No.	Loss on drying (%) at 105°C	Angle of repose	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausners ratio
F1	0.25±0.05	25.3±0.05	0.45±0.04	0.57±0.02	14.4±0.02	1.23±0.02
F2	0.21±0.02	27.4±0.01	0.45±0.09	0.54±0.06	16.7±0.03	1.20±0.05
F3	0.24±0.07	26.2±0.09	0.47±0.02	0.55±0.07	17.7±0.04	1.18±0.07
F4	0.22±0.04	25.5±0.09	0.46±0.08	0.55±0.08	17.6±0.06	1.20±0.05
F5	0.21±0.02	26.6±0.07	0.46±0.05	0.55±0.02	16.9±0.03	1.18±0.03
F6	0.24±0.08	27.0±0.08	0.45±0.023	0.54±0.04	16.8±0.04	1.21±0.02
F7	0.26±0.02	26.6±0.02	0.46±0.03	0.55±0.05	16.9±0.01	1.18±0.01
F8	0.24±0.05	26.3±0.03	0.42±0.09	0.59±0.03	17.4±0.04	1.23±0.07

Table 4: Solubility of ambroxol HCl in different solvents

S. No.	Solvents	Solubility
1	0.1 N HCl	3.66 µg/ml
2	P.B. pH 6.8	22.098 µg/ml
3	P.B. pH 7.4	57.37 µg/ml
4	Distilled water	3.911 µg/ml

which enables proposal to be made for the shelf life of the dosage form and to recommend storage conditions. The purpose of stability studies is to ascertain how the quality of a medicinal product varies as a function of time and under the influence of variety of environmental factors. On the basis of the information thus obtained, storage conditions are recommended which will guarantee the maintenance of the quality of the medicinal product, in relation to its safety, efficacy, and acceptability, throughout the proposed shelf life (i.e., during storage, distribution, dispensing, and use).[2,19]

EXPERIMENTAL DESIGN

For optimization of Ambroxol sustained release tablet, 2^3 randomized full factorial designs were selected. The design was applied to study the effect of concentration of rice bran wax, DCP, and MCC on formulation. The amount of rice bran wax (X1) and the amount of MCC (X2) and the amount of DCP (X3) were selected as independent variables, in this study. These 3 factors were evaluated at two levels as higher and lower levels with coding +1, and −1, respectively.[20,21]

The general polynomial equation for 2^3 factorial designs is

$$Y = B_0 + B_1(x_1) + B_2(x_2) + B_3(x_3) + B_{12}(x_1x_2) + B_{13}(x_1x_3) + B_{23}(x_2x_3) + B_{123}(x_1x_2x_3)$$

Where, Y is dependent variable, B0 arithmetic mean response of nine batches, and B1 estimated coefficient for factor X1. The main effects (X1, X2, and X**3**) represent the average result of changing one factor at a time from its low to high value. The interaction term (X1, X2, and X**3**) shows how

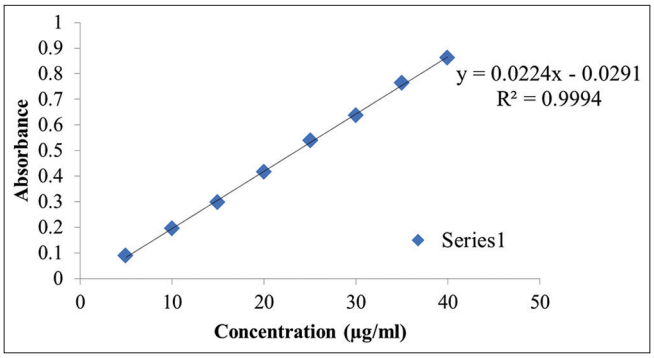

Figure 2: Calibration curve of ambroxol hydrochloride in 0.1 N HCl

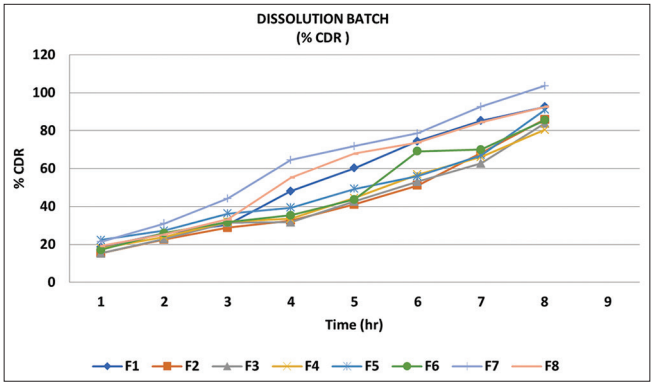

Figure 3: Dissolution study of batches F1-F8

the response changes when three factors are simultaneously changed. The polynomial terms ($X1^2$, $X2^2$, and $X2^3$) are included to investigate non-linearity.[2]

The data demonstrate that both X1 (RBW) and X2 (MCC) and X3 (DCP) affect the time required for drug release. From the results, it can be concluded that, and increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X1, X2, and X3 levels.[4] .

RESULTS

They were evaluated by physicochemical properties and results show in following Table 2.

Construction of calibration curve by UV–visible spectrophotometric method

Accurately weighed 10 mg of Drug "A" was dissolved in sufficient amount of pH 1.2 buffers, 0.5% SLS and volume was made to 10 mL with it. Different concentrations were prepared in the range of 4–20 µg/mL by diluting the stock solution with pH 1.2 buffer, 0.5% SLS, that is, dissolution medium. The absorbance values were measured at 235 nm against dissolution medium as blank and CC were constructed [Figure 2].

The λ max value for the sample in 0.1 N HCL was found to be 244 nm which was as per the reported value and the drug purity got confirmed.

Solubility

The granules were evaluated by bulk density, tapped density, bulkiness, angle of repose, compressibility index, and Hausners ratio to determine for micromeritic properties and results are presented in Table 3.

Formulation evaluated by the following test

To study weight variation test according to USP/NF, the test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average.

Tablet requires certain amount of mechanical strength or hardness, which was measured by Monsanto Hardness Tester. Ten tablets were randomly picked from batch formulation batch and evaluated for hardness during manufacturing and expressed in kg/cm². For each batch, five tablets were used. The thickness of tablet and diameter was measured by digital Vernier caliper apparatus.

Friability was determined by the ten reweighed tablets that were placed in the Roche friabilator, which were then operated for 100 revolutions (25 rpm). The tablets were, then, dusted and reweighed. The tablets that loss <1.0% of their weights are generally considered acceptable.

Dissolution test

Medium

0.1N HCL for 2 h, pH 6.8 Phosphate Buffer, 900 mL.

Apparatus

Type I, 50 rpm.

Drug release studies were carried out using an USP type I dissolution apparatus with 900 mL of the dissolution medium maintained at 37 ± 1°C for 8 h, at 50 rpm, 0.1 N HCl (1.2) was used as dissolution medium for first 2 h followed by pH 6.8 phosphate buffers for further 6 h. 5 mL of sample was withdrawn at predetermined time intervals replacing with an equal quality of drug free dissolution fluid. The samples were filtered through 0.45 µ membrane filter, and drug content in each sample was analyzed after suitable dilution by UV/Vis spectrophotometer at 248 nm, and cumulative percent drug release was calculated. Dissolution study of batches F1-F8 as shown in Figure 3. Solubility of ambroxol HCl in different solvents given in Table 4.

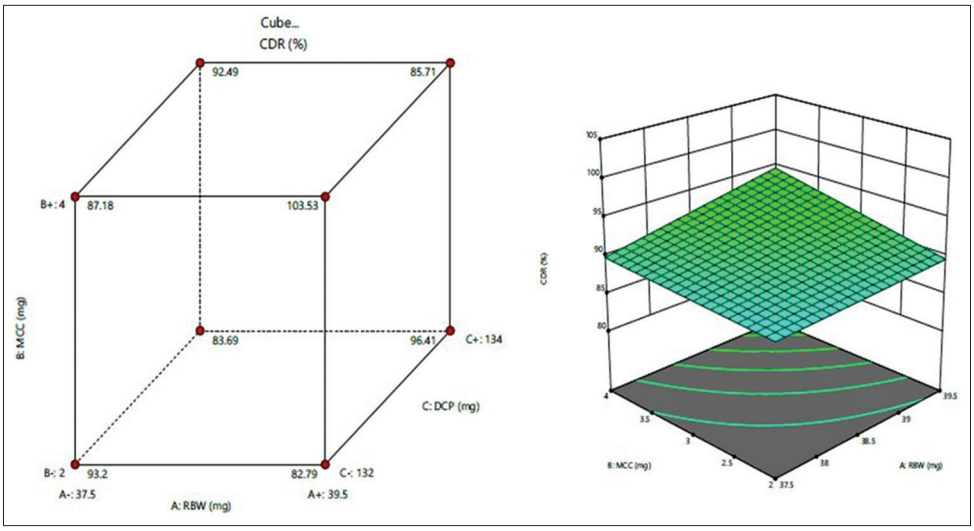

Figure 4: Contour plots, cube, and 3D response surface plots showing relative effects of different process parameter on % cumulative drug release

Table 5: ANOVA for selected factorial model: Response 1: CDR

Source	Sum of squares	df	Mean square	*F*-value	*P*-value	
Model	355.62	6	59.27	612.29	0.0309	Significant
A-RBW	17.64	1	17.64	182.25	0.0471	
B-MCC	20.54	1	20.54	212.23	0.0436	
C-DCP	8.82	1	8.82	91.12	0.0665	
AB	6.59	1	6.59	68.06	0.0768	
BC	34.53	1	34.53	356.69	0.0337	
ABC	267.50	1	267.50	2763.41	0.0121	
Residual	0.0968	1	0.0968			
Cor total	355.72	7				

Table 6: Fit statistics

SD	0.3111	R^2	0.9997
Mean	90.63	Adjusted R^2	0.9981
C.V. %	0.3433	Predicted R^2	0.9826
		Adeq precision	71.2635

Statistical evaluation of experimental design

The best fit model obtained by design expert for each response was evaluated on the basis of ANOVA by calculating the F value and statistical significance of the data was performed in terms of regression coefficients. It was observed that the best fitted model. ANOVA for selected factorial model: Response 1: CDR as shown in Table 5.

The model F-value of 612.29 implies the model is significant. There is only a 3.09% chance that an F-value this large could occur due to noise.

From results of the optimization studies, it was observed that, as concentration of polymer increases, there are increases the release of drug. In these cases, A, B, C, AB, BC, and ABC are significant model terms [Table 6]. The polynomial equation of response R1 showing the combine effect of RBW, MCC, and DCP on cumulative drug release. In this equation, magnitude of A and B is high as compare to C, variable A and B showing positive effect for cumulative drug release (Concentration of polymer increases % CDR is also increasing). Magnitude of C is low as compare to A and B. It showed negative effect [Figure 4].

Final equation in terms of coded factors

CDR = +90.63+1.48 A+1.60 B–1.05 C+0.9075 AB–2.08 BC–5.78 ABC [Table 7].

The effect of tablet composition, as such there was impact seen on batch no. F7 the rate of drug releases. Moreover, applied factorial design model was shows that F7 batch was optimized batch. Compression parameters of trial F1, F2, F3, F4, F5, F6, F7, and F8 as shown in Tables 8-11.

Table 7: Stability observations (40ºC/75%RH) of optimized trial F7

Tests	Specifications	Initial	1 month	3 months
Description	white colored, biconvex tablets	Complies	Complies	Complies
Identification	The retention time of the principal peak obtained in sample should be concordant with that of working standard.	Complies	Complies	Complies
Water by KF	NMT 2%w/w	0.83	0.85	0.96
Medium: 0.1N HCL for 2 h	3 h. 20–50%	3 h. 48	3 h. 51	3 h. 49
Then Ph 6.8 Phosphate Buffer, 900 mL	6 h. 35–65%	6 h. 82	6 h. 89	6 h. 84
Apparatus: Type I, 50 rpm	8 h. NLT 75%	8 h. 99	8 h. 98	8 h. 98
Assay	Drug A b/w 90% and 110% of labeled amount of drug A	99.3	90.44	90.70

Table 8: Compression parameters of trial F1, F2, F3, F4, F5, F6, F7, and F8

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	Standard
Hardness (kg/cm^2)	5±0.15	5.5±0.17	6.5±0.10	7.5±0.15	8±0.17	7.5±0.18	6.5±0.11	7.1±0.15	5–8 kg/cm^2 as per IP
Thickness (mm)	5±0.05	5.6±0.07	5.2±0.05	5.5±0.06	5±0.04	5.3±0.08	5.6±0.03	5.8±0.06	---------
Friability (%)	2.5±0.04	1.2±0.05	0.66±0.06	0.84±0.06	1.02±0.08	0.93±0.06	0.9±0.04	1.02±0.07	<1% as per IP
Weight variation (mg)	240±4.07	244±5.04	24±2.5	249.8±2.07	245.2±3.87	247±3.65	246±4.51	246±6.09	250 mg

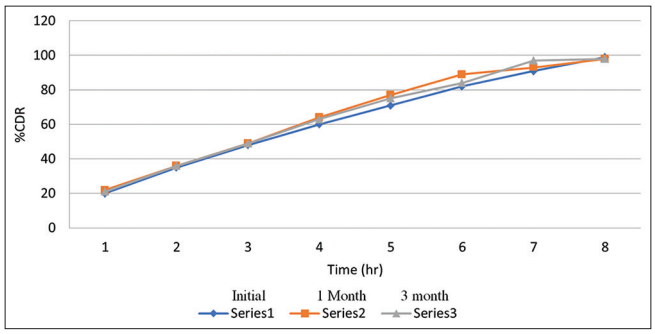

Figure 5: Stability sample dissolution result at 40°C/75% RH

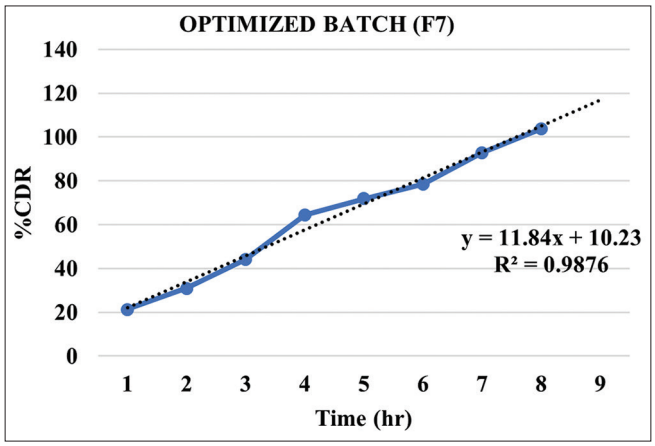

Figure 6: Graphical presentation of optimized formulation

Table 9: Powder flow characteristics

Powder flow characteristic of tablet blend		
S. No.	**Parameter**	**Value**
1	Bulk density (g/mL)	0.46 g/mL
2	Tapped density (g/mL)	0.55 g/mL
3	Compressibility index (%)	17.6%
4	Hausners ratio	1.20
5	Angle of repose	26.6

Table 10: Evaluation of optimized formulation of tablet

S. No.	Parameter	Results
1	Hardness	6.5 kg/cm^2
2	Thickness	5.6 mm
3	Friability	1.2%
4	Weight variation	246 mg

Evaluation of optimized batch

The effect of tablet composition, as such there was impact seen on batch No. F7 the rate of drug release. % Drug release of all batches as shown in Table 6.

Dissolution study of optimized formulation

Similarity factor study between tablets and theoretical release shows a f2 factor larger than 50 at each time

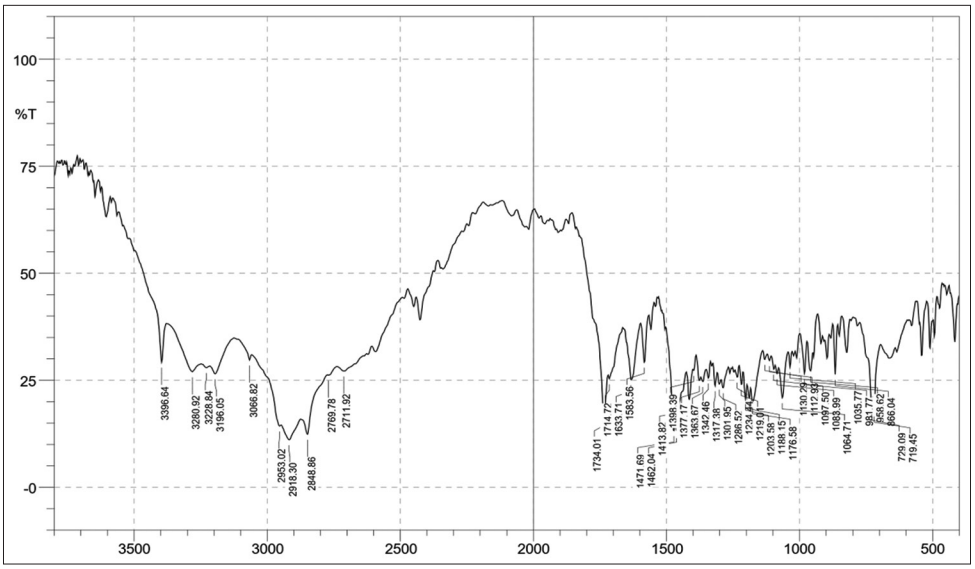

Figure 7: Infrared spectrum of formulation

Table 11: Release kinetic model and coefficient of correlation (R^2)

S. No.	Release kinetic model	Coefficient of correlation (R^2)
1	First order	0.9919
2	Zero order	0.9938
3	Higuchi	0.9939
4	Hixon-Crowell	0.9688
5	Korsmeyer-peppas	0.975

point, averaging 80.18. Tablets' f2 factor averaged over 50, however at 3rd and 4th hours it was below 50. In-vitro tablet release was compared to the predicted profile. Comparing formulation and theoretical release patterns, we found a tight match. So, F7 was regarded an optimum formulation because these tablets did not display any burst release and extended the release for 12 hours with a theoretical release pattern. The above formulas were chosen for expedited stability investigations.

Pharmacokinetic drug release study

The drug released data were evaluated by the graphically. *In vitro* released data were fitted into various mathematical models such as zero order, first order, Hixson-Crowell, Higuchi, and Korsemeyer-Peppas model to understand the mechanism of drug released and the released rate from the dosage form.

Stability study

The stability studies of final trial was done for 1, 2, and 3 months by packing in HDPE container in humidity chamber (40°C/75% RH, 30°C/75% RH, and 25°C/60% RH). The result given in Table for 1 month and 3 months shows that all parameters of formulation including physical parameters, impurity profile, content uniformity, or dissolution profile were within specification limit. Hence, it indicates that optimized formulation trial is stable. Stability sample dissolution result at 40°C/75% RH as shown in Figure 5.

Stability study was done on the optimized formulation (F7) for 3 months. The formulation was exposed to accelerated conditions, that is, at 40°C/75% RH. Later, the study proceeded to evaluate the tablets for dissolution to know if there is any change observed or whether the formulation remains stable. Graphical presentation of optimized formulation as shown in Figure 6.

Infrared (IR) spectroscopy

The IR spectrum of drug sample was recorded at a resolution of 4 cm^{-1} over range 4000–400 cm^{-1} and principle peaks were measured using SHIMADZU 8400 FT-IR (Japan) spectrophotometer.

It gives the interpretation of the peaks of mixture of drug and polymer obtained in the IR spectra along with their corresponding functional group. From the FTIR spectra, it is observed that the peaks at 3396 cm^{-1} indicate presence of OH starching in alcohol groups. The peak 2953 cm^{-1} confirms presence of CH stretching in cyclic compounds which are present in fatty compounds, 1714, 1471 cm^{-1} indicates presence of C=O, OH-C=O carboxylic acid compound presents, then 1064, 1035 cm^{-1} indicates presence of alkane stretch and bending CH_3 containing ester group. Infrared spectrum of formulation as shown in Figure 7 and Table 13.

Table 12: % Drug release of all batches

Time in h	F1% CDR	F2%CDR	F3%CDR	F4%CDR	F5%CDR	F6%CDR	F7%CDR	F8%CDR
1	18.68	15.42	15.23	17.9	22.32	17.23	21.42	19.21
2	25.64	22.56	22.87	23.91	27.26	25.96	31.05	25.13
3	30.37	28.77	31.51	32	36.18	31.82	44.24	33.19
4	48.08	32.57	31.76	33.47	39.36	35.37	64.53	55.33
5	60.29	41.09	42.69	44.43	49.32	43.78	71.84	68.04
6	74.54	51.17	53	56.7	55.96	69.08	78.56	73.81
7	85.21	68.23	62.81	66.06	67	69.96	92.8	84.43
8	92.6	85.9	83.8	80.6	91.03	85.5	103.64	92.6

Table 13: Peak and chemical group present in infrared spectrum of formulation

Peak cm^{-1}	Chemical group
3396	O-H stretching
2953	CH aldehyde
1714	C=O ketone
1633	C=C ester
1471	C=O stretching
1064	C-C alkane stretch
1035	C-O-C ester

CONCLUSION

Sustained released tablet of ambroxol hydrochloride were prepared using natural polymer rice bran wax. The following evaluations were performed for the powder blends and tablets, IR spectral studies, dissolution studies, and stability. The results of powder blends and evaluation of tablets test showed that all the parameter is within the limits. IR spectroscopic studies indicated that the drug is compatible with the highest proportion of the polymer. When comparing all formulations, F7 showed the sustained release of 103% at the end of 8 h. Kinetic analysis showed that all the formulations followed first-order release and follows the mechanism of both diffusion and erosion. The stability studies proved that there was no significant change in drug content and *in vitro* drug release. From the above study, it was concluded that ambroxol hydrochloride can be formulated as sustained release tablet using rice bran wax.

ACKNOWLEDGMENT

The authors are thankful toMedley Pharmaceuticals Andheri, Mumbai for providing gift sample of ambroxol hydrochloride and Balaji Mill Mumbai for rice bran wax and also grateful to the management of the KBHSS institute of pharmacy for providing facilities to carry out the research work.

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Source of Support: Nil. **Conflicts of Interest:** None declared.